MAIL STOP APPEAL BRIEF-PATENTS
Attorney Docket No.: 27391U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

	BRUECK-SCHEFFLER	Conf. No.:	2887
Serial No.:	10/582,499	Art Unit:	1627
Filed:	June 9, 2006	Examiner:	CARTER, K.

For: **AQUEOUS SUSPENSIONS OF CICLESONIDE FOR NEBULISATION**

REPLY BRIEF

This Reply Brief is filed in response to the Examiner's Answer mailed October 25, 2011. Pursuant to 37 C.F.R. §1.193(b)(1), a Reply Brief may be filed within two (2) months of the date of the Examiner's Answer, making this Reply Brief due on or before December 25, 2011. Accordingly, this paper is timely filed.

1. Status of Claims

The status of the claims is as follows upon filing of this Reply Brief:

Claims cancelled: 11

Claims withdrawn from consideration but not cancelled: 21-41

Claims pending: 1-10 and 12-20

Claims objected to: None

Claims allowed: None

Claims rejected: 1-10 and 12-20

The claims on appeal are 1-10 and 12-20.

2. Grounds of Rejection to be Reviewed on Appeal

A. Rejection of claims 1-4, 7-10 and 12-20 under 35 USC § 103(a)

Whether the identified claims are unpatentable under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628).

B. Rejection of claim 5 under 35 USC § 103(a)

Whether the identified claim is unpatentable under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Allen et al. (J. Allergy Clin. Immunol., Sept. 2003, vol. 112, no. 3, pp. s7-s40) and ACS Registry (Feb. 1995, p. 1).

C. Rejection of claim 6 under 35 USC § 103(a)

Whether the identified claim is unpatentable under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Sambuco et al. (US 2005/0175546).

3. Arguments

A. Rejection of claims 1-4, 7-9 and 12-20 under 35 USC § 103(a)

The Examiner has maintained the rejection of the identified claims under 35 U.S.C. § 103(a) as unpatentable over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628).

Appellant again respectfully traverses the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief regarding the patentability of the rejected claims. In addition, appellant provides the following reply showing how and why the Examiner's assertions are in error.

No prima facie case of obviousness has been properly established

Appellant again respectfully submits that a *prima facie* case of obviousness has not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the divergent teachings of Nishibe et al., Saidi et al. and Lintz et al.; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

There is no motivation to combine the Nishibe et al., Saidi et al. and Lintz et al. references with any reasonable expectation of success

Appellant continues to disagree that the Examiner has demonstrated how a person of ordinary skill in the art would be motivated to combine the cited references

with any reasonable expectation of success. In view of their divergent teachings, a person of ordinary skill in the art would not be motivated to combine the cited references.

The Nishibe et al. reference outlines the problems associated with autoclaving a suspension which comprises a water-insoluble drug such as a corticosteroid. Therefore, starting with the Nishibe et al. reference, the person of ordinary skill in the art is faced with the technical problem of providing a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. This problem is due to the difficulties associated with autoclaving a corticosteroid suspension. In particular, Nishibe et al. address the issue of "drug content uniformity" in paragraph [0014] and explain that the uniformity "of [an] aqueous suspension containing a water-insoluble drug tends to be depressed by autoclaving, even if the drug is chemically stable."

The Examiner has tried to remedy the deficient teachings of the Nishibe et al. reference with the Saidi et al. reference. As such, the Examiner has attempted to use a reference that does not even teach autoclaving (i.e. Saidi et al.) to provide the ordinary skilled artisan with the requisite motivation to solve the technical problems *associated with* autoclaving – namely, to provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration.

As appellant put forth in the Appeal Brief, Saidi et al. teach compositions disclosed that are all sterilized by use of a 0.22 micron sterile filter and not by autoclaving. Indeed, sterilizing the suspension of Nishibe et al. through the filtration

method of Saidi et al. would result in the **loss** of the ciclesonide in suspension. Thus, one of ordinary skill would certainly not look to the filtration method of Saidi et al. to remedy the deficiencies of the autoclaving method of Nishibe et al.

Further, the compositions of Saidi et al. are "formulated such that they contain the corticosteroid active agent(s) in a ***dissolved*** state." (emphasis added) *See* col. 5, lines 34-35. Again, appellant notes that the methods of the presently pending claims are directed to preparing ***suspensions*** of ciclesonide sterilized through ***autoclaving*** suitable for nebulization. In contrast, the methods of Saidi et al. are focused on ***solutions*** of corticosteroids sterilized through ***filtration***. Again, one of ordinary skill would not look to a reference teaching a ***solution*** of an active sterilized through ***filtration*** to modify a method of preparing a ***suspension*** of an active sterilized through ***autoclaving***.

The same reasoning applies to the secondary Lintz et al. reference. The compositions of Lintz et al. contain "a sterile aqueous liquid capable of dissolving the solid composition for said liquid pharmaceutical composition." *See* paragraphs [0012] and [0016] of Lintz et al. Again, appellant notes that the methods of the presently pending claims are directed to preparing ***suspensions*** of ciclesonide sterilized through ***autoclaving*** suitable for nebulization. In contrast, the methods of Lintz et al. are focused on ***dissolving*** the solid composition to form a liquid composition that is sterilized through ***filtration***. Again, one of ordinary skill would not look to a reference teaching a ***solution*** of an active sterilized through ***filtration*** to modify a method of preparing a ***suspension*** of an active sterilized through ***autoclaving***.

Therefore, a person of ordinary skill in the art would not look to the Lintz et al. reference to remedy the deficient teachings of Nishibe et al. and/or Saidi et al. to arrive at the presently pending claims.

Appellant further notes the Examiner's statements in the paragraph bridging pages 12-13 of the Examiner's Answer, in relevant part:

> "The Examiner disagrees [that there is no motivation to combine the references] because the motivation to combine the references is to make a sterile inhalation formulation of ciclesonide.
>
> ...
>
> Therefore to make the nebulizer formulation of ciclesonide, one can use the sterile formulation of Nishibe et al. and add the osmolality agent and surfactant of Saidi et al."

Appellant respectfully submits that the Examiner has seemingly ignored the requirement that the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Thus, it is not enough for the Examiner to simply state that a person of ordinary skill would be motivated to arrive at the presently claimed subject matter without pointing to a teaching within the cited references as to **how** a person of ordinary skill might achieve this result with a reasonable expectation of success.

Arriving at the presently claimed subject matter is not a simple as taking "the sterile formulation of Nishibe et al. and [adding] the osmolality agent and surfactant of Saidi et al." as alleged by the Examiner on page 13 of the Examiner's Answer. This fact becomes quite clear when reviewing the data contained in the instant specification

which will be discussed in detail *supra*. Specifically, the data contained in the specification clearly shows that the ionic and non-ionic osmotic agents – taught to be equivalent by Saidi et al. – are anything but equivalent in obtaining a formulation that is "suitable for nebulization" as required by the presently appealed claims.

Accordingly, it is appellant's position that the Examiner has used improper hindsight reconstruction when she combined the teachings of the Nishibe et al., Saidi et al. and Lintz et al. references in alleging that the presently pending claims are obvious.

There is no teaching in the Nishibe et al., Saidi et al. and Lintz et al. references to select only non-ionic agents

Assuming *arguendo* that a person of ordinary skill would look to the combined teachings of Nishibe et al., Saidi et al. and Lintz et al., it is clear that they would find absolutely no teaching within these references to select only the presently claimed "non-ionic" agents to arrive at the presently pending claims.

Appellant respectfully notes that Saidi et al. at column 7, lines 3-9 generally teaches the addition of an osmotic agent such as sodium chloride and glucose. Thus, Saidi et al. teaches the possible addition of an osmotic agent generally with no recognition that the presently claimed non-ionic agents provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Specifically, Saidi et al. teach that "such agents include **any** low molecular weight water-soluble species pharmaceutically approved for pulmonary and nasal delivery such as **sodium chloride** and glucose." (emphasis added).

Further, Example 5 of Saidi et al. actually compares solutions with and without sodium chloride. The results of the study of Example 5 show very little difference between those solutions containing a 0.9% sodium chloride solution and those that do not contain such a 0.9% sodium chloride solution. *See* Example 5 at cols. 12-13 of Saidi et al. Thus, a person of ordinary skill in the art, upon consulting the Saidi et al. reference, would note that ionic agents such as sodium chloride may be ***perfectly acceptable agents*** for inclusion in a nebulized formulation.

However, it is clear from a careful reading of the instant specification that ionic osmotic agents such as sodium chloride – indeed even in the same concentration as that disclosed as acceptable in Saidi et al. – do not successfully render the presently claimed "sterile aqueous suspension of ciclesonide suitable for nebulization". In this regard, appellant respectfully notes that in Example 7 on page 11 of the instant specification, a comparison was made between two formulations:

Formulation I contained 0.05% micronized ciclesonide, 0.025% Polysorbate 20 as suspending agent **and 0.9% sodium chloride**.

Formulation VII contained only 0.05% micronized ciclesonide and 0.025% Polysorbate 20 as suspending agent.

After sterilization of each Formulation, it was shown that the suspension that contained no ionic agent (i.e. sodium chloride) exhibited no significant increase in the particle size. Conversely, the suspension containing the ionic agent rendered "Large white agglomerates". ***Such agglomerates are not suitable for nebulization.*** In this regard, appellant respectfully notes that **MPEP 2143.01** clearly states that, regarding motivation to properly combine or modify references, a proposed modification cannot

render the prior art unsatisfactory for its intended purpose. If it does, then there can be no suggestion or motivation to make the proposed modification. See **MPEP 2143.01.**

Clearly, Saidi et al. do not appreciate the significance of using only non-ionic agents for adjusting the osmolality of suspensions containing actives such as ciclesonide. As such, Saidi et al. can be viewed as teaching away from suspensions containing only non-ionic agents for adjusting osmolality. Further, the teaching contained in Saidi et al. regarding the possible acceptability of sodium chloride would render the prior art unsatisfactory for its intended purpose.

In view of the clear lack of teaching or suggestion contained in the cited references regarding the selection of **only** non-ionic agents in the presently claimed method, the presently pending claims are not obvious over the cited references.

In Response to the Examiner's statements on page 15 of the Examiner's Answer, appellant respectfully notes the following. The Examiner has attempted to rebut appellant's position by stating:

> [E]xample 5 does not use ciclesonide nor compare it with glucose so it cannot be compared. In regards to Appellants' Example 7, the tests are between a formulation comprising sodium chloride and another formulation not containing sodium chloride. This is not a true comparison with the closest art.
>
> Third, one skilled in the art would have the ability and skill to test for the best osmotic agent to render the best result for nebulization based on the teachings of Nishibe et al., Saidi et al., Lintz et al. and Sambuco et al. Selection of a known material based on its suitability for its intended use is obvious."

Appellant respectfully disagrees with the Examiner's statements.

Regarding the Examiner's seeming assertion that, because example 5 of Saidi et al. does not use ciclesonide nor compare it with glucose, the disclosure contained in

example 5 is somehow not probative, appellant wholeheartedly disagrees. Appellant respectfully notes that the probative value of example 5 of Saidi et al. is not at all weakened because it does not use ciclesonide nor compare it with glucose. Rather, example 5 of Saidi et al. clearly shows that a person of ordinary skill in the art, upon reading Saidi et al., would be motivated to use the ionic agent sodium chloride to adjust the osmolality because of the acceptable results achieved. This fact underscores the clear weakness of the Examiner's reliance on Saidi et al. for its mere general teaching of both ionic and non-ionic osmotic agents in her attempts to establish a *prima facie* case of obviousness against the presently pending claims which are limited to non-ionic excipients.

Similarly, appellant disagrees with the Examiner's statement regarding appellant's Example 7. The Examiner seems to be missing the point. It is not necessary for appellant to make a direct comparison of each of the osmotic agents disclosed in Saidi et al. to demonstrate that the ionic agents taught by Saidi et al. are unsuitable for using in the presently claimed method.

Appellant is using the data contained in the specification to rebut any alleged *prima facie* case of obviousness. Again, the Examiner has relied on Saidi et al. for its teaching of osmotic agents, but Saidi et al. makes no distinction between ionic and non-ionic osmotic agents. Appellant's data clearly demonstrates that the presently claimed subject matter is non-obvious over the teachings of Saidi et al. since it shows that the ionic osmotic agent sodium chloride taught as suitable by Saidi et al. is not suitable for use in a nebulizable formuation as presently claimed.

Finally, regarding the Examiner's statement that "one skilled in the art would have the ability and skill to test for the best osmotic agent to render the best result for nebulization based on the teachings of Nishibe et al., Saidi et al., Lintz et al. and Sambuco et al. Selection of a known material based on its suitability for its intended use is obvious", appellant again disagrees. The Examiner has completely ignored the requirements of MPEP 2143.01 by casting aside appellant's arguments and data contained within their specification that shows that the ionic osmotic excipient sodium chloride as taught by Saidi et al. is unacceptable and would "render the prior art [i.e. Nishibe et al.] unsatisfactory for its intended purpose". Thus, the Examiner's statement that appellant is merely selecting a known material based on its suitability for adjusting osmolality has no merit.

As such, for at least these reasons, claims 1-4, 7-10 and 12-20 are not obvious under 35 U.S.C. §103(a) and appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the present rejection of pending claims 1-4, 7-9 and 12-20.

B. Rejection of claim 5 under 35 USC § 103(a)

The Examiner has maintained the rejection of the identified claims under 35 U.S.C. § 103(a) as unpatentable over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Allen et al. (J. Allergy Clin. Immunol., Sept. 2003, vol. 112, no. 3, pp. s7-s40) and ACS Registry (Feb. 1995, p. 1).

Appellant again respectfully traverses the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief regarding the

patentability of the rejected claims. Appellant respectfully submits that none of the cited references, alone or in combination, render appellant's pending claim 5 obvious.

The Examiner relies on Allen et al. and the ACS registry only to show metabolites of ciclesonide. However, the Allen et al. reference and the ACS Registry do not remedy the deficient teachings of these cited references. Allen et al. and the ACS Registry do not provide the proper motivation to modify a suspension sterilized through autoclaving with the teachings of references directed to solutions of actives sterilized through filtration. Further, Allen et al. and the ACS Registry do not provide any motivation to selected only non-ionic agents to be included in the suspensions of Nishibe et al.

In view of the clear lack of teaching or suggestion contained in the cited references regarding the selection of only non-ionic agents in the presently claimed method, the presently pending claims are not obvious over the cited references.

Therefore, a person of ordinary skill in the art would not look to Allen et al. and the ACS Registry to remedy the deficient teachings of Nishibe et al., Saidi et al. and/or Lintz et al. to arrive at the presently pending claims.

Accordingly, it is improper hindsight reconstruction for the Examiner to combine the teachings of the Nishibe et al., Saidi et al., Lintz et al., Allen et al. and the ACS Registry references to allege that the presently pending claims are obvious.

As such, claim 5 is not obvious under 35 U.S.C. §103(a) and appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the present rejection of pending claim 5.

C. Rejection of claim 6 under 35 USC § 103(a)

The Examiner has maintained the rejection of the identified claims under 35 U.S.C. § 103(a) as unpatentable over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Sambuco et al. (US 2005/0175546).

Appellant again respectfully traverses the rejection and incorporate herein by reference in its entirety all arguments presented in the Appeal Brief regarding the patentability of the rejected claim. Appellant respectfully submits that none of the cited references, alone or in combination, render appellant's pending claim 6 obvious.

Sambuco et al. does not address any of the technical problems associated with autoclaving - namely to provide a sterile aqueous ciclesonide ***suspension*** that does not suffer from clogging and a suspension that is suitable for ***nebulization***. The only disclosure contained in Sambuco et al. regarding autoclaving is a cursory identification of autoclaving as one of many processes that can be used to manufacture sterile formulations for inhalation. See paragraph [0010] of Sambuco et al.:

> [0010] Various processes can be used to manufacture sterile pharmaceutical formulations for inhalation. For example, the active ingredient can be sterilised by dry heating or irradiation, followed by preparation of the formulation under aseptic conditions, or the formulation can be pre-prepared and sterilised by treatment in an autoclave or by filtration.

Further, Sambuco et al. has no teaching that would motivate the skilled artisan to select only the presently claimed "non-ionic" agents to arrive at the presently pending claims.

Sambuco et al. therefore, has no teaching that would cure the deficiencies of the Nishibe et al., Saidi et al. and Lintz et al. references. Therefore, a person of ordinary skill in the art would not look to Sambuco et al. to remedy the deficient teachings of Nishibe et al., Saidi et al. and/or Lintz et al. to arrive at the presently pending claims.

Accordingly, it is improper hindsight reconstruction for the Examiner to combine the teachings of the Nishibe et al., Saidi et al., Lintz et al., and Sambuco et al. references to allege that the presently pending claims are obvious.

As such, claim 6 is not obvious under 35 U.S.C. §103(a) and appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the present rejection of pending claim 6.

Accordingly, appellant respectfully requests that the Board of Patent Appeals and Interferences reverse all rejections of claims 1-10 and 12-20 and remand the case to the Examiner to issue a Notice of Allowance of all pending claims 1-10 and 12-20.

Respectfully submitted,
THE NATH LAW GROUP

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